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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,715	03/04/2005	Stefan Golz	Le A 35 949	3124

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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,715	GOLZ ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' response, received on 27 November 2007, to Office Action of 27 July 2007 has been entered. Claims 1-11 are pending. Claims 2 and 3 have been amended and the amendments made of record. Claims 1-11 are currently under consideration.

Withdrawn Rejections

The rejection of Claims 2 and 3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendment to the claims.

Maintained Rejections

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 1-11 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record and reasons set forth below.

Applicant traverses the rejection. The reason for the traversal are:

a. Applicant's previous responses argued that FPRL1 is highly expressed in cardiovascular tissues, thereby indicating an association between FPRL1 and cardiovascular disease and that post-filing date art supports the specifications's

disclosure that the FPRL1 ligand lipoxin A4 is involved in cardiovascular diseases, respiratory diseases and genito-urological disorders

b. an organ such as the heart comprises various subcompartments in which expression of a gene could be different. The mRNA extracts of heart used to obtain the expression data represent the mean expression from all subcompartments. Thus, applicant argues, a higher expression in the left ventricle as a whole does not permit one to conclude that there is no association between FPRL1 and cardiovascular disease. Applicant's argument has been fully considered but has not been found to be persuasive. It has not been established that there is any specific cardiovascular disease associated specifically with the left ventricle.

c. no undue experimentation is required to screen for activators or inhibitors. However, the issue raised in the previous Office Action was not whether one could screen for activators or inhibitors. This argument has been fully considered but is not deemed persuasive because the issue at hand is whether an agonist or antagonist would be effective as a therapeutic agent to treat recited diseases (see discussion below)

Applicant's arguments have been fully considered but are not found to be persuasive for reasons of record and for reasons set forth below.

As set forth in previous Office Actions, Applicant has not established a nexus between an FPRL1 polypeptide and cardiovascular diseases (the elected species) in general and/or a specific cardiovascular disease. The specification and/or the art also fails to establish a connection between FPRL1 structure, expression or activity or changes in structure, expression or activity and any specific cardiovascular disease condition or pathology. A nexus between an FPRL1 polypeptide and COPD, asthma and genitor-urological disorders in general or a specific disorder has not been established nor has the specification and/or the art established a connection between FPRL1 structure, expression or activity or changes in structure, expression or activity and any specific lung or genitor-urological condition, disorder or pathology.

The applicant has listed a wide range of disorders of different etiologies, progressions and outcomes as ones that may be treated by agents identified by the methods of the instant invention [paragraphs 0228, 0235, 0236, and 0239]. Table 1, a table of relative expression of FPRL1 in various human tissues confirms teachings in the art, that FPRL1 is expressed in a wide variety of tissues. With respect to cardiovascular tissue, expression levels range from a low of 241 in heart to a high of 2048 in heart ventricle. With respect to lung tissue, expression levels range from 750 in fetal lung to 3616 in lung tumor. With respect to genitor-urological tissue, expression levels range from 286 in prostate tissue to 7181 in placenta. One of ordinary skill in the art would not detect a pattern of unique expression of FPRL1 RNA in any one specific tissue or organ system, much less in the cardiovascular system, respiratory system or uro-genital system. Therefore, one would not conclude that a higher expression of FPRL1 mRNA in left ventricle would indicate that modification of FPRL1 signaling would be a useful therapeutic approach to treatment of any and all heart disease. The evidence presented here constitutes an invitation to further experimentation to determine the role of FPRL1 in diseases of any of the organ systems recited in the claims. It would require undue experimentation on the part of the artisan to first identify a disease connected with aberrant FPRL1 signaling, determine whether disease condition is associated with aberrant increased signaling, or aberrant decreased signaling, and then screen for therapeutic agents using the methods of the instant invention.

With respect to post-filing date art presented with response of 10 May 2007:

Levy (2006. Circulation 114:873-875) teaches that myocardial production of 15-epi-LXA, a ligand of the FPRL-1 receptor, is increased by statin drugs (page 873, 1st column). These ligands display potent anti-inflammatory properties (page 873, 2nd column). The figure on page 874 teaches that activation of the ALX receptor (the FPRL-1 receptor) by its ligand (15-epi-Lipoxin A_4) initiates a signaling cascade which inhibits agonist initiated phospholipase D, phosphatidylinositol 3-kinase and reactive

oxygen species generation. Thus, the reference teaches that activation of FPRL1 receptor by its ligand would have the therapeutic effect of inhibiting agonist-induced production of reactive oxygen species. This teaches away from the enablement of the claims of the instant invention as Claims 2 and 3 are directed to methods of screening for a test compound which inhibits the activity of the FPRL1 polypeptide. One of ordinary skill in the art, aware of the teachings of Levy, would be unable to predict that a compound which inhibits FPRL1 activation would be a therapeutic agent useful in the treatment of cardiovascular disease.

Rodgers et al (2005. Am. J. Pathol 167:683-694) teach LXA_4 (the ligand of the FPRL1 receptor) modulated the expression of many PDGF genes and thus acts as a modulator of matrix accumulation and profibrotic change and suggest a potential protective role in progressive renal disease (abstract). Thus, LXA_4 can counteract and diminish the effects of PDGF-stimulated genes responsible for profibrotic activity (page 691, 2nd column). The reference is specifically directed to gene expression in human renal mesangial cells, not to all genitor-urological tissues. One of ordinary skill in the art would conclude, from the teachings of Rodgers et al., that activation of FPRL1 by its cognate ligand would be required for LXA_4-mediated inhibition of PDGF-stimulated gene expression and any resulting therapeutic effects. The skilled artisan, aware of the teachings of Rodgers et al, would be unable to predict that a compound which inhibits FPRL1 activation, as recited by the claims of the instant invention, would be a therapeutic agent useful in the treatment of genitor-urinary disease.

Wu et al. (2006. Am J Respir Cell Mol Biol 34:65-72) teach connective tissue growth factor (CTGF) plays an important role in pathways leading to lung fibrosis via the mitogenic action of CTGF on fibroblasts (abstract). LXA_4 inhibits CTGF-induced proliferation of human lung fibroblasts (HLF) (page 67, 1st column, 3rd paragraph). Pretreatment with PTX, which inhibits signaling by the LXA_4 blocked the inhibitory effects of LXA_4 on CTGF-induced proliferation of HLF suggesting that ALXR mediated the action of LXA_4 on HLF (page 69, 1st column, 1st paragraph). As discussed above, this teaches away from enablement of the claims of the instant invention as Claims 2 and 3 are directed to methods of screening for a test compound which inhibits the

activity of the FPRL1 polypeptide. The skilled artisan, aware of the teachings of Wu et al, would be unable to predict that a compound which inhibits FPRL1 activation, as recited by the claims of the instant invention, would be a therapeutic agent useful in the treatment of asthma or COPD.

In summary, art presented by applicant teaches away from enablement of the claims of the instant invention. Each references teaches stimulation of the FPRL1 receptor to effect an anti-inflammatory response. Therefore, one of ordinary skill in the art would not predict that screening for compounds that inhibit FPRL1 signaling (as recited in independent claims 2 and 3 would identify a therapeutic agent useful in the treatment of cardiovascular diseases, COPD, asthma and genitor-urological disorders.

Therefore, the rejection is maintained.

35 U.S.C. § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1, 2, 4, 5 and 10 under 35 U.S.C. § 102(b) as being anticipated by Gronert et al (1998, J Exp Med. 187:1285-1294) is maintained for reasons of record and for reasons set forth below.

Applicant traversed the rejection. The reasons for the rejection is that independent claims 1 and 2 each recite a step which refers to particular disorders which are not disclosed by Gronert et al.; therefore, Gronert et al does not anticipate the claims.

Applicant's arguments have been fully considered but have not been found to be persuasive. Applicant has presented no new arguments in traversal of the rejection. Thus, the rejection is maintained for reasons of record.

Applicant has not provided evidence of a nexus between changes in FPRL1 structure, expression or activity and any disease condition and therefore has not provided an enabling disclosure. The post-filing date art does not overcome the deficiencies of the disclosure. Therefore, only the actual method steps are considered in formulating the rejection and the teachings of Gronert et al anticipate the limitations of claims 1, 2, 4, 5 and 10.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 1-6, 8-10 under 35 U.S.C. 103(a) as being unpatentable over Gronert et al in view of Fiore et al (1994, J Exp Med. 180:253-260) is maintained for reasons of record.

The rejection of Claim 7 under 35 U.S.C. 103(a) as being unpatentable over Gronert as applied to claim 1 in view of Ramakrishnan (US PGPub 2002/0058259, filed 14 March 2001) is maintained for reasons of record.

The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Gronert et al in view of Seo et al (1997, J Immunology 158:1895-1901) is maintained for reasons of record.

Applicant traversed the rejection. The reason for the traversal is that there is no *prima facie* case of obviousness because Gronert et al do not disclose a connection between the recited polypeptide and any of disease recited in the bodies of independent claims 1 and 2. None of the secondary references remedies this deficiency.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant has presented no new arguments in traversal of the rejection. Thus, the rejection is maintained for reasons of record.

As stated above, Applicant has not provided evidence of a nexus between changes in FPRL1 structure, expression or activity and any disease condition and therefore has not provided an enabling disclosure. The post-filing date art does not overcome the deficiencies of the disclosure. Therefore, only the actual method steps are considered in formulating the rejection.

Conclusion:

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer, Ph.D./
Examiner, Art Unit 1647

/Lorraine Spector/ Ph.D.
Primary Examiner, Art Unit 1647